New Anesthesia Drugs
Already here or on the Horizon

LTC Peter D. Strube
CRNA MSNA APNP ARNP DNAP(c)
Assistant Professor Rosalind Franklin University

Things are in evolution and only getting faster and faster!

Dedicated to:

Thomas G Healey, RN, CRNA, MA
St Mary’s University
Died January 5, 2014
Navy Corpsman Vietnam

Financial Disclosure

There is no financial conflicts with this presentation.

Lecturing about a topic does not constitute endorsement of any product. Please take the time to research each topic for more information.

Mentioning a product or company does NOT represent endorsement.
Think outside the BOX
We can no longer sit by the wayside, we must make ourselves better. Keep a OPEN Mind!

Multimodal
Synergy
Preemptive
Standard, Policy, Guideline, Suggestion???
Zofran
FDA and Codeine?

FDA Alerts!

Tablets
Sprinkles
Topamax®
(topiramate)
Comfort Zone

Most of us practice our art in the comfort zone

New and different ideas tend to pull people from the comfort zone to the scare zone

Try new things
Enhance your patient outcomes

AFE – September 29, 2014 (presentation)
Dr. B Leighton, Cooper, Otto (abstract fall 2013)

41 G6P3-39 weeks at 31 min ACLS: Given A-OK at 1mg/8mg/30mg
Survived and left hospital with small neuro deficits

28 G2P1-39 weeks at ?? Min ACLS: Given A-OK at 0.8mg/4mg/30mg
Survived with no neuro issues

Thromboxane/serotonin
Use this in conjunction to current treatments.
At this time this is a adjunct to get the patient to return to circulation.
Can you do an anesthetic without narcotics?

Not Everything is it appears? Labor Epidurals going away?

Blair et al. Patient-controlled analgesia for labor using remifentanil: a feasibility study

Remifentanil PCA with a bolus dose in the range 0.25-0.5 µg kg and a lockout time of 2 min appears a safe and effective drug for use in labor in patient-controlled analgesia systems.

Is Nitrous Back? 2009

The position of the American College of Nurse-Midwives that women should have access to a variety of measures to assist them in coping with the challenges of labor. Among these should be nitrous oxide, which is commonly used in many other countries.
Crazy?

Think outside the BOX—Think Differently!

Old Drugs, New Ways
New Drugs, Old Battles!

Pharmacogenetics----Micron Technology
Dogma?
Dogma is a principle or set of principles laid down by an authority as incontrovertibly true. It serves as part of the primary basis of an ideology or belief system, and it cannot be changed or discarded.

Massive Transfusion
Early Recognition of Massive Transfusion (MT) Patients
Most patients requiring emergency unmatched blood in ED will need MT

Predictors (3/4 70% 4/4=85% of MT)
- SBP <110 mmHg
- HR > 105
- HCT <32
- pH < 7.25

1:1:1
Tranexamic Acid

New to Ortho World

A competitive inhibitor of plasminogen, and in high concentrations a non-competitive inhibitor of plasmin

- Less transfusions - reported 50%
- Trauma: Antifibrinolytic agent

Increased trauma survival in prospective analysis

- Can’t have blood products, Hextend in same line
- Give within 3 hours - 1gm in 100ml NS over 10 mins
- Then start infusion of 1gm in 100ml NS over 8 hours
- Pump rate 12.5ml/hr
- Further doses can be given, though not supported by literature
New MH Drug? Ryanodex

The drug, an injectable suspension of dantrolene sodium, will be available in 250 mg single-use vials containing the active ingredient in a lyophilized powder.

According to Eagle Pharmaceuticals, Ryanodex can be prepared and administered in less than one minute, compared with 15 to 20 minutes for conventional dantrolene.

The cost for a patient receiving Ryanodex treatment for a MH crisis (based off 2.5mg/kg in a 70kg patient) is $1,610 versus $700 with generic dantrolene. This cost does not include additional doses of dantrolene that will be required.

This research and orphan drug status is leading to additional research... for example for heat stroke:

Side Effects: MDMA--Ecstasy

Succinylcholine (X is a trigger) should be used cautiously given the risk of compounded the malignant hyperthermia like effects of the drug, raising intracranial pressure and potentially worsening hyperkalemia.
Fospropofol (Lusedra)

Approved by the FDA on 12/12/08 a pro-drug of propofol
Same mechanism of action; except has a slow, smooth and predictable rise in concentration

By Definition: this is a sedative-hypnotic aqueous agent indicated for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures.

NOT FOR GENERAL

This will and has already raised some concern—FDA states that only those trained in delivering anesthesia should use this drug. What about the ago old question??

What about using this in GI clinic?

Fospropofol (Lusedra)

- Standard monitoring
- IV dosing adults: 6.5mg/kg - followed by supplemental dosing of 1.6mg/kg as needed
- Initial dose should not exceed 16.5 ml (35mg/cc)
- 90 kg x 16.5 = 585mg
- Supplemental doses should not exceed 4ml; each additional doses should only be given when needed and no more frequent than every 4 minutes
- Dose range 60-90 kg
- Not for Kids
- Greater than 65 years of age give 75% of dose
- For every 1.86mg administered one mg of propofol is created
- What is special: earlier “clear headed”
Remimazolam

► Analogue of Midazolam
  ► that utilizes the ester design.
► Broken down by nonspecific ester hydrolysis
► Designed for outpatient procedures as well as EGD/C-Scope area
► Linear Clearance superior to Versed
► Better sedation with less side effects of Versed
  ◦ respiratory and cardiac events

► 6mg loading Dose followed by 3 mg maintenance doses
► Crazy but initial studies have not change in ventilation or oxygenation with remimazolam with NO supplemental oxygen applied

Etomidate --MOC

Methoxycarbonyl-etomidate (MOC-etomidate), a new compound derived from the anesthetic etomidate, is as fast-acting and provides the same hemodynamic stability as its parent drug, but does not cause dangerous adrenal gland suppression as etomidate can

In the human liver cells, the researchers found that the MOC-etomidate had an in-vitro half-life of 4.4 minutes versus more than 40 minutes for etomidate, and produced carboxylic acid as its only detectable metabolite

MOC-etomidate is an etomidate analogue that retains etomidate’s important favorable pharmacological properties. However, it is rapidly metabolized, ultra-short, acting, and does not produce prolonged adrenocortical suppression following bolus administration
Carboetomidate
► Analogue of etomidate
► When compared to MOC it has slow onset and difficult to formulate.
► ??? Benefit ???

Phaxan

Water-based clear, colorless solution that is easy to manufacture.
Like propofol, the current standard for intravenous anesthesia, Phaxan™ is a fast onset and offset intravenous anesthetic but, unlike propofol, there is no accumulation with repeat dosing.
Phaxan™ is twice as potent as propofol but it causes less blood pressure fall than propofol with a six times higher safety margin.
A clinical trial involving dose finding and comparison with propofol was commenced in December 2013.
Interesting thought... old stuff coming back??
Dexamethasone

- Steroids are useful as adjuvant therapy for pain
- Steroids can directly reduce pain in concert with opioid use and allow for a reduction in dose
- Steroids reduce pain by inhibiting prostaglandin synthesis
- Steroids have been shown to reduce spontaneous discharge in an injured nerve, which reduces neuropathic pain.

What if we could add it to our Blocks? Increase our Duration!

Anesthesiology. 2011;115:575-88
De Oliveira GS Jr, Almeida MD, Benzon HT, McCarthy RJ

- Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials
- Doses of 0.1 mg/kg or less are great for PONV but don’t help with pain relief.
- Doses of about 0.15 mg/kg cover PONV and reduce postoperative pain and opioid demand.
- Doses above 0.2 mg/kg don’t get you any more pain relief. An exception may be greater pain relief with movement (e.g. early ambulation in total joint patients?).
- Giving dexamethasone preoperatively improves pain relief considerably more than giving it after induction. (Optimally 1-2 hours before incision.)
- In general, we need not worry about side effects with 0.15 mg/kg any more than we do with current PONV doses.

Effect of dexamethasone on the duration of interscalene nerve blocks with ropivacaine or bupivacaine

K. C. Cummings 1,2,3, T. I. Nunes 1,2,3, L. F. Neville 1,2,3, A. L. Watson 1,2,3, J. J. Brena 1,2,3, and D. J. Sanders 1,2,3

1. Department of Anesthesiology and Pain Medicine, 2. University of Washington, Seattle, WA, USA
3. Department of Anesthesiology, Pain Medicine, and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, WA, USA

Background: Pain after shoulder surgery is often treated with interscalene nerve blocks. Single-injection blocks are effective, but time-limited. Adjuncts such as dexamethasone may help. We have studied the hypothesis that adding dexamethasone prolongs the duration of epidural and interscalene analgesia and that the magnitude of this effect increases with increasing duration of intervention.

Effect of dexamethasone on the duration of interscalene nerve blocks with ropivacaine or bupivacaine

K. C. Cummings 1,2,3, T. I. Nunes 1,2,3, L. F. Neville 1,2,3, A. L. Watson 1,2,3, J. J. Brena 1,2,3, and D. J. Sanders 1,2,3

1. Department of Anesthesiology and Pain Medicine, 2. University of Washington, Seattle, WA, USA
3. Department of Anesthesiology, Pain Medicine, and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle, WA, USA

Background: Pain after shoulder surgery is often treated with interscalene nerve blocks. Single-injection blocks are effective, but time-limited. Adjuncts such as dexamethasone may help. We have studied the hypothesis that adding dexamethasone prolongs the duration of epidural and interscalene analgesia and that the magnitude of this effect increases with increasing duration of intervention.
Emend (Aprepitant) PDNV

- A new class of antiemetics is born -- NK-1 receptor antagonists
- Does not interfere with other antiemetics
- No dosage adjustments for hepatic or renal compromise
- Does not effect QT segments
- Use in caution with CYP3A4 (warfarin) drugs; this is typically related to a three day course in chemo-related treatments
- Decreases efficacy of hormonal contraceptives
- Anesthesia is a single dose; 40-80mgs
- Expensive single 80mg dose is $125

Emend (Aprepitant)

- This is a additional adjunct treatment to those refractory to PONV
- Most side effects are related to prolonged and high doses with little evidence that any effects are related to a single anesthesia dose
- Top adverse experiences in patients with general anesthesia were:
  - Anemia, bradycardia, flatulence, hypotension, pruritus, pyrexia
- Expensive ; Expensive; Expensive; Expensive
- Two additional NK-1 Drugs: Casopitant, Rolapitant
Rolapitant

VARUBI is a substance P/neurokinin 1 (NK1) receptor antagonist indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting.

The recommended dosage is 180 mg Rolapitant administered approximately 1 to 2 hours prior to the start of chemotherapy.

Administer in combination with dexamethasone and a 5-HT3 receptor antagonist,

Akynzeo

Akynzeo, a combination product of netupitant and palonosetron

Each capsule contains 300 mg of netupitant and palonosetron hydrochloride equivalent.

Marinol

MARINOL should not be used if you are

► allergic to dronabinol or any of its ingredients, including marijuana and sesame oil

► Most patients respond to 5 mg three or four times daily.

► Marinol has been shown to provide increased pain relief when taken in combination with opioid pain relievers, according to ClinicalTrials.gov. The active ingredient in Marinol, THC, is believed to bind with pain receptors to reduce the transmission of pain through the spinal cord and brain.
Olanzapine as an antiemetic:
is an atypical antipsychotic that belongs to the
thienobenzodiazepine class.

Olanzapine cost:
- Rapidly disintegrating tab 5mg: ~ $1.00
- Rapidly disintegrating tab 10mg: ~ $1.15
- Tab 5mg: $0.10
- Tab 10mg: $0.20
- IM injection: $25.25

We only have a very small amount of information about the use of olanzapine IV,
and none of it in the periop period............

Most Studies looked at it as compared to Zofran..............

Palonosetron (Aloxi)
► A new 5HT-3 receptor antagonist
► Remember: this group of drugs compete with
serotonin to block binding at the serotonin receptor binding site
► When the binding site is blocked the ion channel on the receptor closes
and calcium influx is stopped, blocking signals to the brain that trigger
nausea and vomiting
► What is special about this 5HT-3???
► Aloxi binds with both the serotonin site but also a allosteric binding
site; this action increases the overall affinity for aloxi by triggering a
conformational change. This change also causes a receptor
internalization and induces a prolonged inhibition of serotonin binding
to the cell surface receptors.

Aloxi
► What is cool about it??  40 hour plasma half life
► Small single dose --- 0.075 mg single dose
► Easy to remember dose timing -- before induction of anesthesia in
preop over 10 seconds ( will cover why shortly)
► NO information for Peds or OB
► Warnings:.... do not mix with other drugs
► Flush line before and after admin  ?? PKA – weak acid vs. weak base
► Risks: 5% QT prolongations; bradycardia 4%; Headache3%
► Headache (remember imitrex)
Versed

Anesthesia and Analgesia 2016; 122:656

Meta-Analysis of studies from 1974-2014

Drastically reduced PONV, especially with preop and small dose 30 minutes before extubation.
The last 30 minutes Versed

Non-Pharmacologic Methods for PONV
- Acupuncture—really exciting information!
- Acupressure
  - over “P6” point of wrist (3cm prox. to distal wrist crease, between the tendons of palmaris longus and flexor carpi radialis).
  - over K-99 acupuncture point (middle phalanx of 4th finger) applied bilaterally
- Alcohol Pad—Queese Ease!

Oxygen
- Hypoxia triggers cortical afferents which triggers the vomiting center which leads to the act of vomiting
- One specific study showed a decreased rate of PONV
- A second study trying to prove the first could not either prove or disprove the first study
- Increased O2 levels (less than 80%) in orthopedics have been shown to decrease infection rates in total joints
- Interesting thoughts?
Oxygen

Hypoxia triggers cortical afferents which triggers the vomiting center which leads to the act of vomiting.

Perioperative clinical factors & immune function

- Supplemental perioperative oxygen improves postop outcomes
- FiO2 of 0.8 doubles subcut O2 tension & halves postop wound infection rate
- Supplemental O2 ↓ PONV after laparoscopies & laparotomies

Curr Opin Anesthesiology 2006;19:11-18

Pre-operative Alvimopan (Entereg)

- μ-Opioid antagonist that is restricted from crossing the blood-brain barrier
- Blocks peripheral and central side effects (e.g., nausea, constipation) without compromising CNS activity
- Oral dosing
- Low systemic absorption
- High μ-receptor affinity
- Appropriate for patients with chronic pain

(Republished with permission of Wolters Kluwer Health, Inc. from Wang AA, Dermine JG. Entereg [Alvimopan]. ON THE TABLE 2007;2(1):5-7.)
Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures

As an Updated Report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters

Minimum preoperative fasting for healthy people

Clear liquids – two hours
- Water, fruit juice without pulp, clear tea, black coffee

Light meal (toast + liquid) – six hours

Regular meal (fried or fatty food) – eight hours

Pre-operative PO fluid
The BEST treatment of choice for beta-blocker overdose is?

A. Glucagon
B. Methylene Blue
C. Esmolol
D. Vasopressin

Glucagon

- Glucagon is produced in the alpha cells of the pancreas.
- Glucagon enhances the formation of cAMP.
- Glucagon is used to increase myocardial contractility and heart rate in the setting of beta-blocker toxicity.
- Glucagon enhances automaticity in the nodal conduction system without increasing automaticity in the ventricles (unlike sympathomimetics).
- Glucagon stimulates catecholamine release and has been used as a diagnostic tool in pheochromocytoma.
- Dose:
  - IV: 1–5 mg
  - Infusion: 25–75 mcg/min

Glucagon must be reconstituted immediately prior to administration.
Hypotensive Thought Pattern

- What is your order for treating Hypotension????
  - 0 fluids
  - 1 and 2; Neo and ephedrine
  - 3 methylene blue
  - 4 epi chip shots (5-10mcg)—Guy Weinberg Paper!
  - 5 vasopressin
- What is 6 for you?
- ?? Glucagon

Hemodynamic Effects of Methylene Blue

Methylene blue, a commonly used tissue marker, is normally hemodynamically inert. However, for a variety of clinical scenarios associated with an inflammatory response, methylene blue results in increases of systemic blood pressure, systemic vascular resistance (SVR), and myocardial contractility.

The application of methylene blue’s effects is also being studied in the management of numerous clinical scenarios, including:

- vasoplegia
- anaphylactic shock
- septic shock
- hypotension from ACE-I/ARBs
- hemodialysis hypotension
- cardiogenic shock

Dosing of Vasopressin

**Intraoperative hypotension**
- Dilute with 19 mL NS in a 20 cc syringe to create a concentration of 1 unit/mL.
- Administer 0.5 – 1 unit to treat hypotension in an adult.

**Septic Shock**
- Exogenous vasopressin has been used in patients with septic shock in several studies. AVP infusion (0.01–0.04 U/min) increased peripheral vascular resistance and arterial blood pressure within minutes of application. No increase in pulmonary vascular resistance or pulmonary artery pressure was reported in patients treated with low-dose vasopressin (0.04 U/min), nor were cardiac complications or changes in electrolyte, blood and urine osmolality, or metabolic variables.
Shortage

Reason for the Shortage
American Regent discontinued vasopressin injection in early 2015.1,2 Par Sterile Products (formerly JHP) discontinued Pitressin injection in November 2014. Par Sterile Products introduced Vasostrict injection in November 2014. This is the only FDA-approved vasopressin injection. Fresenius Kabi will discontinue distributing vasopressin on March 15, 2015. A letter is available regarding this discontinuation.


Available Products
Vasostrict Injection, Par Sterile Products 20 units/mL, 1 mL multi-dose vial, 25 count (NDC 42023-0164-25)


New Pain Drugs

► Ofirmev
► Caldolor
► Sufentanil Patch
► Nucynta
► Remoxy
► Mexiletine
► Antidote: Entereg (almivopam)

Multimodal Approach to Acute Pain Management


Mild Pain
- Acetaminophen, NSAIDs, or COXIBs
- Local/regional anesthesia

Moderate Pain
- Low dose of opioids
- Acetaminophen, NSAIDs, or COXIBs
- Local/regional anesthesia

Severe Pain
- Higher doses of opioids
- Entereg (almivopam)
OFIRMEV $10.00/1000mg

- IV acetaminophen injection: Cadence Pharm (Cadence was bought out, price spike)
- Minimum dosing interval is every 4 hours
- Administer over 15 min... well... ??????
- www.ofirmev.com
- Do not exceed max daily doses: Adult is 4 grams per day; Pediatric is dosed at 15mg/kg with max of 75 mg/kg/day

Regional Anesthesia Pain Management 2015 discusses that the purchase by Mallinckrodt increased the price by 285%, costing the healthcare system nearly $2.78 Million in inflation costs.

Liver issues is big
- Contraindicated in patients with liver failure/hepatic injury or with known hypersensitivity to acetaminophen...
- What about ETOH?
- Common side effects are: N/V; HA; insomnia; constipation, pruritus and agitation and atelectasis
- Using this drug may mask post surgical fever when used for post-operative pain.
Ibuprofen-Caldolor $10

- Think about Ketorolac: Actions and side effects
  - Big differences... Less action on Cox 1 and more Cox 2 action...
  - What does this mean? Less bleeding... More pain control can give anytime during the surgery... better now that we can give per-op
  - 400mg/4ml or 800mg/8ml
  - Dilute and administer over 30 minutes
  - 400mg-800mg Over 30 min repeat every 6 hours PRN*

- Fluids = "well hydrated prior to use"

Pain Control with an Old Drug?

Phantom pain... Calcitonin

Calcitonin is a 32-amino acid peptide hormone which regulates calcium homeostasis in vertebrates. It also has analgesic properties, primarily through receptor-mediated modulation of serotonergic pain pathways in the central nervous system. A meta-analysis concluded that calcitonin was effective in the treatment of complex regional pain syndrome and systematic reviews reported benefit in the treatment of acute vertebral fracture pain. A randomized controlled trial (RCT) showed calcitonin was effective in the treatment of acute phantom limb pain. However, a Cochrane review did not support its use in the treatment of metastatic bone pain although a single RCT's findings were promising.

The drugs are aimed at a compound called calcitonin gene-related peptide or CGRP. Four different companies are testing drugs that affect CGRP: Alder Pharmaceutical, Amgen, Eli Lilly and Company, and Teva Pharmaceuticals. CGRP is a neurotransmitter -- a message-carrying chemical.
One or two doses of IV calcitonin 200 IU

Alkermes Pharm—Meloxicam IV

Meloxicam IV/I.M is a proprietary, Phase III-ready, long-acting COX-2 NSAID used to target moderate to severe acute pain. Meloxicam IV/I.M is a nonsteroidal anti-inflammatory drug. In five phase II studies treating more than 700 patients with acute pain, meloxicam IV/I.M demonstrated positive effect on treating rapid onset of pain relief and "time to peak" analgesic effect, 18 to 24 hour duration of pain relief as well as favorable tolerability.

Recro Pharm Dex-IN

Recro's Dex-IN, an intranasal form of dexmedetomidine, which has been tested as an analgesic drug for post-operative pain. Last year the company's lead drug passed a Phase Ib trial that demonstrated its proof of concept in providing effective pain relief. However, in September Recro Pharma halted a trial of its lead product candidate Dex-IN.

The company decided to stop the trial because it does not believe the study would achieve "statistical significance" in its current design. Recro Pharma has an upcoming interim analysis of ongoing Post Op Day 1 Phase II trial for Dex-IN, and depending on clinical success, the possibility for two proprietary compounds to enter Phase III by year end.
Sufentanil $3.52/50mcg

- 5 - 10X more potent than fentanyl
- Sufentanil 0.0035 mg = fentanyl 0.05 mg
- Safe therapeutic index: 25,211
- Dose: .025 - 30 µg/kg
- Analgesic dose: 0.1 - 0.4 µg/kg IV
- Maintenance dose: 1µg/kg followed by 0.25-0.5 µg/kg/hr
- High dose: 10 - 30 µg/kg

- New PATCH coming out from Durrect Pharm....

Fentanyl Patch

- Transdermal Patch
- Technology changing for delivery
- On Demand? : Fentanyl iontophoretic transdermal system provides a 40 mcg dose of fentanyl per activation on-demand
- Other fentanyl thoughts:
  - BUCCAL TABLET; BUCCAL SOLUBLE FILM; SUBLINGUAL TABLETS; NASAL SPRAY; SUBLINGUAL SPRAY

Fentanyl

**The Patch!**

Clonidine produces a dose-dependent impairment of baroreflex-mediated thermoregulatory responses to positive end-expiratory pressure in anesthetized humans.

Clonidine was clinically evaluated to suppress postoperative shivering in 60 patients who had undergone anesthesia for general, thoracic, and vascular surgery. The study was carried out in double blind conditions with comparison of two doses (75 and 150 micrograms) of clonidine.

**Exelon (rivastigmine) possible muscle relaxant interaction ****

A Drug used for the treatment of Alzheimer's and is a cholinesterase inhibitor. Complete action is unknown!

Rivastigmine, an acetyl cholinesterase inhibitor, may be administered orally or as a transdermal patch for treatment of Alzheimer's disease and may interfere with neuromuscular blocking drugs.


**Macrocrion Technology**

**Drugs---IROKO Pharm**

ZORVOLEX is the first low dose FDA-approved NSAID developed using proprietary SoluMatrix Fine Particle Technology™.

ZORVOLEX contains diclofenac as submicron particles that are approximately 20 times smaller than their original size. The reduction in particle size provides an increased surface area, leading to faster dissolution.

ZORVOLEX was developed to align with recommendations from FDA and other professional medical organizations that NSAIDs be used at the lowest effective dose for the shortest possible duration consistent with individual patient treatment goals. For more information, visit www.zorvolex.com.
Nanoparticles:
Recent article:

Nano anesthesia: A Novel, Intravenous Approach to Ankle Block in the Rat by Magnet-Directed Concentration of Ropivacaine-Associated Nanoparticles

Anesthesia and Analgesia: April 2014

Exparel

► EXPAREL is a local analgesic that utilizes bupivacaine in combination with the proven product delivery platform, DepoFoam®. A single intraoperative injection given at the close of surgery delivers postsurgical pain control with reduced opioid requirements for up to 72 hours

► Following its release from the DepoFoam® particles, the rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site

a pivotal soft tissue trial of EXPAREL versus placebo, patients experienced a 30% reduction in cumulative pain scores and a 45% reduction in opioid consumption
Exparel

Posidur

» New product just like Exparel

» Except Clear.... Could this be trouble?
Lipid Rescue

- 20% lipid solution
- 1.5 ml/kg over 1 minute
- Follow immediately by a infusion at rate of 0.25 ml/kg/min
  (17.5 ml/min for a 70 kg adult)
- Repeat dose if no improvement – and double the infusion rate
- Max of 10 ml/kg???
- www.lipidrescue.org
- ACLS-----limit epi----Weinberg work!
- What about Propofol? (Propofol is 1%)

Mivacurium is coming back...

Gantacurium Phase 2 complete

- Is this a new Generation being born of NMB?
- Based on amino acid pathway—olefinic
- This drug is chemically degraded by rapid adduction to L-cysteine and removes Chlorine
- These two routes make it unavailable to bind to acetylcholine receptor
- Does not require Liver, Kidneys, Temperature or pH
- Two exciting analogs...
- There has always been a search for the new Sxxx....
Gantacurium

- Dose: 0.5 mg/kg
- Fast acting with short duration
- Exciting new group of drugs!
- Key is: NO histamine release!

CW002

- Same pathway as Gantacurium!
- This compound Lacks Chlorine
- Dose: 0.15mg/kg
- Fast acting Intermediate duration
- Key is: NO histamine release!

CW 011

- This is the baby of this group...
- Lacks Chloride so slower to break down
- Dose: 0.10 mg/kg
- Fast acting more intermediate duration
- Key is: NO histamine release!
L-Cysteine

Dissolved in concentration of 200mg/ml

- Antidote for New class of Muscle relaxants
  - Olefinic isoquinolone Diester NMb
  - Only works with new group of NMb's

Cysteine

Human Studies: IV administration of exogenous L-Cysteine induced faster recovery.

Dose in Studies: 5-50mg/kg

- (average dose is 10mg/kg)

Compared to Edrophonium reversal with atropine.
Did not need to give antimuscarinics agent.
Reversed in 1 minute

There are risks…High doses: (added to TPN) but 1-1.5 grams/kg can cause neuro defects reported in infants
Cyclodextrins are poly saccharide compounds that were analyzed as scavenging molecules for toxins and additives for food materials.

Beta Cyclodextrins were developed as vehicles for long acting drugs.

They have been tried as solubilizing agents for various drugs like Propofol, bupivacaine, sufentanil.
Sugammadex--Bridion

- Forms a very tight water soluble complex with steroidal NDMR
- i.e. ROC > VEC > PANC
- It is biologically inactive, does not bind to plasma proteins
- Does not rely on renal excretion
- WE have always mis-used muscle relaxants (first reported 1979)
- IV administration results in rapid removal of free drug from the plasma. This action creates a concentration gradient favoring the movement of the NDMR molecules from the NMJ back into the plasma, where they are encapsulated by free Sugammadex molecules.

Sugammadex

- Does not affect SUXX or benzylisoquinoliniums;
- If after using Sugammadex and paralysis needs to be achieved consider using these drugs
- SIDE EFFECTS: hypotension; coughing (was from a study when given to awake patients) vomiting, nausea, dry mouth, decreased temperature
- Is traditional Neuromuscular function monitoring needed?

Cost of Sugammadex

- 70kg man
- 2mg/kg dose: 140mg, one 2mL vial = $84.93
- 4mg/kg dose: 280mg, one 5mL vial = $155.55
- 16mg/kg dose: 1120mg, two 5mL vials and one 2mL vial = $396.03
- Caveats
  - Uncontracted prices from distributor
  - Patient cost usually approximately 3x this cost

Dose examples: ROC 1.2mg.kg administered and three minutes later 16mg/kg of Sugammadex given, this provides faster onset/offset profile than suxx
Will this change the face of anesthesia?
Sugammadex

Recent FDA Approval

Soon available as 200mg/2mL and 500mg/5mL vials

Calabadion

Gantacurium Paradigm

Source: Full Prescribing Information, Bridion® (Sugammadex). 2015, Merck Sharpe and Dohme Corp.


Novel Reversal Agents

Sugammadex - FDA Saga

2014 Lit review identified 15 cases of hypersensitivity reactions from sugammadex.

All within 5 minutes of administration.

Most common reactions rash and anaphylaxis.

11 patients skin tested, 10 positive

Use of Sugammadex

- Binds Roc > Vec >> Panc
- Dose Depends on Depth - Single Bolus
  - If 2-TOF twitches returned
  - If 1-2 PTC and 0 TOF twitches, 1.2mg/kg
  - If reversal needed as soon as 3 mins after dose, 16mg/kg
- Confirm reversal
- Time = 1.5-3 minutes (mean)
Sugammadex - Adverse Reactions

- Serious but rare:
  - Anaphylaxis
  - Bradycardia
- > 10%:
  - Nausea, Vomiting, Pain, Hypotension, Headache
- Signs of emergence (moving, sucking, chewing)
- Large meta-analysis with > 1500 patients = no significant difference in side effects compared with neostigmine with less residual paralysis

PTT and PT

In response to the FDA's requests, 4 additional studies were conducted examining the impact of sugammadex on coagulation. These investigations demonstrated a small increase in PT and aPTT that occurred within minutes of administration, but resolved within an hour.

In addition, in a large study of patients undergoing hip or knee replacement surgery, no increase in bleeding or transfusion requirements was observed in patients randomized to receive sugammadex.

Sugammadex - Bleeding

- Increases PTT, PT/INR up to 25% for up to 1h in healthy volunteers
- In a study of patients with major lower extremity orthopedics surgery, PTT and PT/INR increases < 10% were noted (did NOT require transfusion)
- No difference in bleeding, anemia incidence
- Concomitant thromboprophylaxis in this study
Cardiac

In order to address concerns related to cardiac arrhythmias, an analysis of phase 2 and 3 clinical studies was conducted, as well as an analysis of post-marketing data.

These study findings indicated that QTc was not prolonged in patients given sugammadex. The studies also indicated that arrhythmias did not occur with greater frequency with sugammadex compared to neostigmine, although bradycardia can occur with both agents.

Sugammadex – Not For Use In

- Children < 18
  - Some rat studies show possible decreased bone development in childhood
- Severe renal impairment (renal excretion)
  - GFR < 30
- Elderly patients exhibit slower recovery

Sugammadex - Bleeding

- Increases PTT, PT/INR up to 25% for up to 1h in healthy volunteers
- In a study of patients with major lower extremity orthopedics surgery, PTT and PT/INR increases < 10% were noted
- No difference in bleeding, anemia incidence
- Concomitant thromboprophylaxis in this study
Sugammadex – Drug Interactions

► Toremifene (SERM) may prolong NMBD recovery
► Other drugs could displace rocuronium
► Physically incompatible with: ondansetron, ranitidine, verapamil

Source: Full Prescribing Information, Bridion® (Sugammadex). 2015, Merck Sharpe and Dohme Corp.

FDA Warns!

FDA also warned about the potential for marked bradycardia, and that some of these cases have resulted in cardiac arrest, often within minutes of giving the drug.

Patients should be closely monitored for hemodynamic changes during and after reversal of neuromuscular blockade, and physicians should give anticholinergic agents, such as atropine, if they observe clinically significant bradycardia, the agency said.

Physicians should also advise women using hormonal contraceptives that the drug may temporarily reduce contraceptive efficacy, so they should use an alternative method of birth control for a period of time after gaining the drug.

The most common adverse reactions with sugammadex included vomiting, hypotension, pain, headache, and nausea.

Recurarization Bottom Line

► (Except in magnesium case) No clinically significant recurarization has been reported when sugammadex is used as labeled according to manufacturer recommendations

► Recurarization can be seen if an inadequate dose is used!!
Package insert

Merck:
7.3 Interaction Potentially Affecting the Efficacy of Hormonal Contraceptives

In vitro binding studies indicate that BRIDION may bind to progestogen, thereby decreasing progestogen exposure. Therefore, the administration of a bolus dose of BRIDION is considered to be equivalent to missing dose(s) of oral contraceptives containing an estrogen or progestogen. If an oral contraceptive is taken on the same day that BRIDION is administered, the patient must use an additional, non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) for the next 7 days.

In case of non-oral hormonal contraceptives, the patient must use an additional, non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) for the next 7 days.

Always Aware

Sugammadex and Hormonal Birth Control Interaction: Identifying and Educating Affected Patients Automatically through Health Link

Sugammadex is a medication indicated for the rapid reversal of neuromuscular blockade induced by rocuronium and vecuronium. It was recently added to the formulary and is restricted to use in the OR and ED. Sugammadex interacts with hormonal birth control, both oral and non-oral formulations, possibly resulting in temporary loss of efficacy of the birth control for up to seven days.

Beginning September 13, 2016 documentation of sugammadex administration by the provider will generate an automatic educational message for women of reproductive potential who are between the ages of 10 and 60 years old. The message informs them that they received sugammadex. It also provides information about the nature of the interaction and the need for back-up birth control for seven days. Condoms and spermicides are recommended.
Portola Pharmaceuticals (Nasdaq:PTLA) today announced that andexanet alfa, a U.S. Food and Drug Administration (FDA)-designated breakthrough therapy, has been granted orphan drug designation by the FDA's Office of Orphan Products Development for reversing the anticoagulant effect of direct or indirect Factor Xa inhibitors in patients experiencing a serious uncontrolled bleeding event or who require urgent or emergent surgery. Currently, there is no approved antidote for these patients.

Praxbind (idarucizumab) for use in patients who are taking the anticoagulant Pradaxa (dabigatran) during emergency situations when there is a need to reverse Pradaxa's blood-thinning effects.

Trial included 123 patients taking Pradaxa who received Praxbind due to uncontrolled bleeding or because they required emergency surgery. In this ongoing trial, based on laboratory testing, the anticoagulant effect of Pradaxa was fully reversed in 89 percent of patients within four hours of receiving Praxbind. In this patient trial, the most common side effects were low potassium (hypokalemia), confusion, constipation, fever and pneumonia.

Others that might impact Anesthesia

- JM-1232 New hypnotic nonbenzo from Japan
- PF0-713 Variant of Propofol
- AZD-3043 Nonbarb hypnotic

Just FDA approved:
Idarucizumab to reverse pradaxa
Factor X concentrate
Thank you!

Email me for the articles: pstrube3000@yahoo.com